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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/828,659 | 04/21/2004 | Yogesh S. Sanghvi | ISIS-5468 | 4925 |
| 32650 | 7590 | 07/31/2006 | EXAMINER | |
| WOODCOCK WASHBURN LLP ONE LIBERTY PLACE - 46TH FLOOR PHILADELPHIA, PA 19103 | | | EPPS FORD, JANET L | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1633 | |
| DATE MAILED: 07/31/2006 | | | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/828,659

Applicant(s)

SANGHVI ET AL.

Examiner

Janet L. Epps-Ford

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-8, 12, and 20, are rejected under 35 U.S.C. 102(b) as being anticipated by Hirschbein.

Claim 1 recites a method of preparing an oligomeric compound comprising (a) providing a 5'-O-protected compound, (b) treating said 5'-O-protected compound with a deprotecting reagent, (c) coupling said 5'-O-protected compound with an activated phosphorous composition, (d) treating said extended compound with a mixture comprising an oxidizing reagent and a capping reagent. Claim 2, method of claim 1 further comprising treating said oligomeric compound with a reagent for a time and under conditions effective to remove said blocking groups. Claim 3, method of claim 2, wherein said reagent is effective to cleave the oligomeric compound from the support media. Claim 4, the method of claim 3, wherein said reagent is aqueous ammonium hydroxide. Claim 5, the method of claim 2, further comprising treating said oligomeric compound with a further reagent for a time and under conditions effective to cleave the oligomeric compound from the support media. Claim 12, method of claim 1, wherein said oxidizing reagent transfers a sulfur atom. Claim 20, the method of claim 1 wherein

said coupling of the 5'-O-deprotected compound with the activated phosphorous composition is performed in the presence of an activating agent.

Hirschbein discloses a method of synthesizing an oligomer comprising deblocking a blocked functionality, usually a 5'-tritylated hydroxyl (steps (a-b) claim 1) on the growing correct-sequence chain, or on the initial monomer attached to a solid phase support, to form a reactive functionality, such as a 5'-hydroxyl. Next the reactive functionality is reacted with a blocked and protected nucleoside phosphoramidite or phosphorothioamidite monomer or analog thereof (coupling step (c) of claim 1), usually in the presence of an activator, such as tetrazole (claims 20-21). The unreacted functionalities are capped (step (d) claim 1), and then oxidized. (col. 4, lines 51-68). The oxidation and capping steps can be reversed. (col. 5, lines 1-4).

Hirschbein used this process for synthesizing a 22-base phosphorothioate (anticipates claims 39-41), except that in place of the oxidation step, a sulfurization step was substituted, in other words, the synthesis consisted of repeated cycles of detritylation, coupling, sulfurization, and capping (col. 5, lines 41-50, anticipates claim 12 since the sulfurization step comprises the transfer of sulfur using a thiuram disulfide). The 22-mer was cleaved from the support and deprotected with concentrated ammonium hydroxide (col 5, lines 62-63; anticipates claims 2-5, 33-34). The sulfurization step comprises, preferably wherein, a thiuram disulfide is delivered to the growing oligomer in a suitable organic solvent, such as acetonitrile, tetrahydrofuran, dichloromethane, or the like in a concentration of 0.01 M to about 2.0 M (col. 5, lines 15-20).

3. Claims 1-6, and 9-11 are rejected under 35 USC 102(b) as being anticipated by Caruthers et al. (US 4,458,066)

Claim 1 recites a method for preparing an oligomeric compound that encompasses (a) providing a 5'-O-protected compound, (b) treating said 5'-O-protected compound with a deprotecting reagent, (c) coupling said 5'-O-protected compound with an activated phosphorous composition, (d) treating said extended compound with a mixture comprising an oxidizing reagent and a capping reagent. Claim 2, method of claim 1 further comprising treating said oligomeric compound with a reagent for a time and under conditions effective to remove said blocking groups. Claim 3, method of claim 2, wherein said reagent is effective to cleave the oligomeric compound from the support media. Claim 4, the method of claim 3, wherein said reagent is aqueous ammonium hydroxide. Claim 5, the method of claim 2, further comprising treating said oligomeric compound with a further reagent for a time and under conditions effective to cleave the oligomeric compound from the support media. Claim 6 recites wherein the method of claim 1 further comprises treating said oligomeric compound with a deprotecting agent to deprotect the T3 hydroxyl protecting group. Claims 9-11 recite the method of claim 1 wherein said oxidizing reagent transfers an oxygen atom, and wherein said oxidizing reagent is iodine. Caruthers et al. disclose a method for synthesizing polynucleotides wherein said method comprises deprotection of a 5'-tritylated nucleoside attached to a solid support via a phosphite linkage between 3'-OH of the nucleoside and the solid support (i.e. silica gel; col. 6, lines 1-7). The deprotected 5'-O of the nucleoside attached to the solid support (compound I, col. 6) is then reacted

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with a 5'-O-protected nucleoside compound comprising a secondary amino group covalently linked to the Phosphorous atom linked to the 3'-O of the nucleoside. The secondary amino group may comprise heterocyclics including tetrazole and unsaturated heterocyclics comprising a ring nitrogen ((col. 7, lines 17-25); see compound R4 of step (c) of instant claim 1). The next step comprises a capping step wherein the unreactive moieties are capped or blocked in order to prevent the formation of several deoxyoligonucleotides with heterogeneous sequences (col. 7, lines 61-68). Oxidation is carried out by reaction with iodine or alternatively with peroxides like tertiary butyl peroxide and benzoyl peroxide (col. 8, lines 38-44). According to Caruthers et al., oxidation should be carried out before further condensation of nucleoside is attempted. Blocking groups are then removed by mild bases, such as ammonium hydroxide (col. 8, lines 50-52). However, the blocking groups can be removed in a step-wise fashion using triethylammonium thiophenoxide in solvent, e.g. dioxane or tetrahydrofuran. Thereafter, the product is treated with ammonium hydroxide to separate the synthesized oligonucleotide from the polymer support by hydrolyzing the ester linkage joining the oligonucleotide to the support (col. 8, lines 54-60).

Caruthers et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

4. Claim 1 is rejected under 35 USC 102(b) as being anticipated by Caruthers et al. (US 5,750,666).

Caruthers et al. disclose a method for synthesizing polynucleotides wherein said method comprises deprotection of a 5'-tritylated nucleoside attached to a solid support

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via acid catalysis (col. 52, lines 54-55). The deprotected 5'-O of the nucleoside attached to the solid support is then reacted with a 5'-dimethoxytrityl nucleoside-3'-aminophosphine (col. 52, lines 56-57). The next step comprises a capping step wherein the unreacted moieties are capped or blocked with acetic anhydride and N-methylimidazole (col. 52, lines 57-59). Oxidation is then carried out by reaction with aqueous iodine (col. 52, lines 59-61). The modified polynucleotide is then cleaved from the support, and the base and phosphate-protecting groups removed by treating the polymer-supported polynucleotide with concentrated ammonium hydroxide, i.e. wherein the protecting groups are base labile and stable in acid (col. 53, lines 38-40). See example XX wherein an oligonucleotide of 18 nucleotides in length was synthesized, comprising the heterocyclic base moiety adenine (col. 53, line 36).

Additionally, in another embodiment of Caruthers et al. the nucleoside monomers, used for coupling to the deprotected 5'-O- of the nucleoside or oligonucleoside attached to the support, comprise a 3'-O activated modified phosphorous group (see compound Ia, col. 3), wherein M is a heteroatom such as sulfur, oxygen or nitrogen (col. 4, lines 59-60), and X is a secondary amino group NR₆R₇, wherein R₆ and R₇ when taken together form (*inter alia*) an alkylene chain, or taken separately represent substituted or unsubstituted alkyl, aryl or aralkyl groups (col. 5, lines 18-30). In another embodiment X can be derived to include a morpholine group (col. 5, line 60).

Caruthers et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

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5. Claims 1-7, 9-12, and 20 are rejected under 35 USC 102(b) as being anticipated by Ravikumar et al.

Ravikumar et al., in one specific example, teach a method for synthesizing oligonucleotides wherein said method comprised covalently attaching a 5'-O-Dimethoxytritylthymidine to CPG (controlled pore glass) through an ester linkage in a glass reactor, and deprotecting the 5'-OH of the attached nucleoside using a solution of dichloromethane and dichloroacetic acid (volume/volume). The product is washed with acetonitrile. Then, a 0.2M solution of 5'-O-(4,4'-dimethoxytrityl)thymidine-3'-O-(2-diphenylmethylsilylethyl N,N-diisopropylphosphoramidite) in acetonitrile and a 0.4M solution of 1H-tetrazole (activator in coupling step, col. 6, lines 64-67) in acetonitrile are added and reacted at room temperature for 5 minutes. The product is washed with acetonitrile, and then a 0.05M solution of Beaucage reagent (sulfur transfer reagent) in acetonitrile is added and reacted at room temperature for 5 minutes. This sulfurization step is repeated one more time for 5 minutes. The support is washed with acetonitrile and then a solution of acetic anhydride/lutidine/THF (1:1:8), and N-methyl imidazole/THF is added to cap the unreacted 5'-hydroxyl group. The product is washed with acetonitrile and then treated with 30% aqueous ammonium hydroxide. This process allowed the synthesis of a 5'-TTTTTTT-3' phosphorothioate heptamer (col. 12, lines 35-60).

It is noted that in regards to the 5'-O-deprotected compound, 5'-O-(4,4'-dimethoxytrityl)thymidine-3'-O-(2-diphenylmethyl-silylethyl-N,N-diisopropylphosphoramidite), the diisopropyl group correspond to L1 and L2 in the formula recited in step (c) of

instant claim 1, and the 3'-O-2-diphenylmethyl-silyethyl group corresponds to R5, X1 or Pg, in the structures recited in claim 1 of the instant application.

The method for synthesizing oligonucleotides as disclosed by Ravikumar et al. may also comprise wherein the oxidizing agent transfers an oxygen atom, for example wherein the oxidizing agent comprises: iodine/ tetrahydrofuran/water/pyridine or hydrogen peroxide/ water or tert-butyl hydroperoxide or any peracid like m-chloroperbenzoic acid (col. 7, lines 43-52).

Ravikumar et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

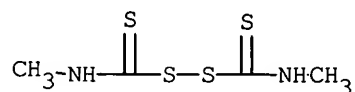
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-8, 12-14, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirschbein.

Claims 13-14 recite the method of claim 12 wherein said oxidizing agent is dimethylthiuram disulfide.

The discussion of Hirschbein set forth above as applied to claims 1-8, 12, and 20 is incorporated here. However, Hirschbein does not explicitly disclose a method for synthesizing an oligomer wherein the oxidizing agent which transfers a sulfur atom is dimethylthiuram disulfide.

Although Hirschbein does not explicitly disclose wherein the sulfur transfer reagent is dimethylthiuram disulfide, Hirschbein does disclose wherein the thiuram disulfides used in the disclosed method of synthesizing sulfurized oligonucleotides preferably has a structure according to formula I (col. 2, lines 46-68). Dimethylthiuram disulfide has the following structure:



This compound is encompassed by formula I of Hirschbein, specifically wherein at least two of any one of R1-R4 are hydrogen, and the remaining groups of R1-R4 are methyl groups. It would have been obvious to one of ordinary skill in the art at the time of filing to modify the method of Hirschbein to specifically comprise the use of dimethylthiuram disulfide as the sulfur transfer agent. One of ordinary skill in the art would have been motivated to make this modification since substituting one of R1-R4 with a methyl group is a preferred embodiment of the Hirschbein invention (col. 3, lines 13-14), and furthermore substituting R1-R4 with hydrogen is also specifically disclosed as a possible substituent for the preferred thiuram disulfide according to formula I. Moreover, Hirschbein clearly suggests that making such substitutions would have produced a compound having similar properties as the dimethylthiuram disulfide compound used in the method of the instant claims, i.e. as a sulfur transfer agent used in phosphorothioate oligonucleotide synthesis (col. 3, lines 54-63).

Therefore, the invention as a whole is *prima facie* obvious over Hirschbein.

8. Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruthers et al. (US 5,750,666) in view of Santamaria et al.

Claim 15 recites the method of claim 1 wherein said capping reagent comprises about one part by volume of acetic anhydride in acetonitrile or tetrahydrofuran, added to about one part by volume of N-methylimidazole and pyridine in acetonitrile or tetrahydrofuran.

The discussion of Caruthers et al. (US 5,750,666) as applied to claim 1 set forth above is incorporated here. However, Caruthers et al. do not teach wherein capping of the synthesized oligomer comprises treating the oligomer with a capping reagent comprising about one part by volume of acetic anhydride in acetonitrile or tetrahydrofuran, added to about one part by volume of N-methylimidazole and pyridine in acetonitrile or tetrahydrofuran.

Santamaria et al. describe an automated method for synthesizing oligodeoxyribonucleotides, wherein the synthesized oligomer is capped using a mixture of capping with acetic anhydride and 1-methylimidazole in tetrahydrofuran and pyridine.

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the method for synthesizing oligonucleotides of Caruthers et al. to utilize a capping reagent comprising about one part by volume of acetic anhydride in acetonitrile or tetrahydrofuran, added to about one part by volume of N-methylimidazole and pyridine in acetonitrile or tetrahydrofuran. One of ordinary skill in the art would have been motivated to make this modification since Santamaria et al. clearly discloses that a mixture comprising acetic anhydride, 1-methylimidazole, tetrahydrofuran and pyridine has specific utility as a capping reagent, and absent evidence to the contrary, it would have been obvious for one of ordinary skill in the art to substitute one functionally

equivalent capping reagent for another. Additionally, although the Santamaria et al. does not expressly define the volumes of each component in the capping reagent as set forth in the instant claims, absent evidence of unexpected results, it would have been obvious for one of ordinary skill in the art at the time of filing to modify the parameters in a given reaction in order to optimize the results. See, MPEP § 2144.05 that states: “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”

Therefore, the invention as a whole is *prima facie* obvious over Caruthers et al. in view of Santamaria et al.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,809,195. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims represent a species of the broad method recited in instant claims 1-20.

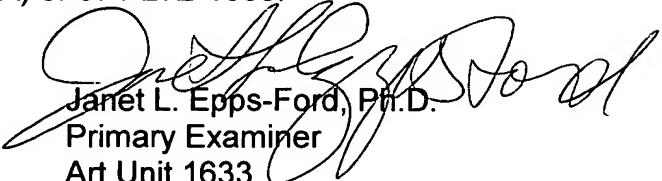
For example, step (d) recited in instant claim 1 (and those claims dependent therefrom) recites a method wherein an extended compound with a mixture comprise an oxidizing agent and a capping reagent for a time and under conditions effective for form said oligomeric compound. However, the claims in the issued patent are limited to wherein the oxidizing agent and the capping reagent are added in the same step for a time and under conditions effective to form said oligomeric compound. The instant claims are interpreted as encompassing wherein the oxidizing agent is added to the extended oligomeric compound, and in another step the capping reagent is added to produce a mixture comprising both the oxidizing reagent and the capping reagent. The issued claims, which represent a species of the instant claims, are considered to anticipate the broader method recited in the instant claims.

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11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


Janet L. Epps-Ford, Ph.D.
Primary Examiner
Art Unit 1633

JLE